2021

The Utility of Gadolinium Contrast Agents in Older Patients with Multiple Sclerosis after Cessation of Disease Modifying Therapy

Liam du Preez
ldupreez@uvm.edu

Adam Ulano
adam.ulano@uvmhealth.org

The Utility of Gadolinium Contrast Agents in Older Patients with Multiple Sclerosis after Cessation of Disease Modifying Therapy

Liam du Preez BS[1], Adam Ulano MD[2], Emily Azalone[3], Andrew Solomon MD[3]

Larner College of Medicine at the University of Vermont, Burlington, VT[1] Department of Radiology at the University of Vermont Medical Center[2], Department of Neurology at the University of Vermont Medical Center, Burlington VT[3]

Abstract

Gadolinium contrast agents are frequently administered during follow-up imaging obtained on patients with multiple sclerosis (MS), a complex autoimmune disease that affects the central nervous system. Recent literature details the deposition of gadolinium in various areas of the brain after long-term repeated exposure. While no negative effects have been documented as a result of gadolinium deposition, efforts are underway to identify patients for which these contrast agents could be safely withheld. MS often becomes quiescent in older patients, allowing cessation of disease modifying therapy (DMT). We hypothesized that encountering enhancing lesions in this cohort is uncommon to the extent that contrast may be unnecessary. We identified the cohort of patients at the University of Vermont Medical Center with a diagnosis of MS, age greater than 55, not on DMTs. We reviewed all of the MRI reports on for each patient performed after the cessation of DMTs provided the patient was older than 55 at the time of the MRI to determine: 1) the presence of new lesions, 2) the presence of enlarging lesions, and 3) the presence of enhancing lesions. Of all reports reviewed, less than 1% demonstrated an enhancing lesion.

Introduction

MS is an autoimmune disease defined by the presence of white matter inflammation and demyelination in the central nervous system (CNS). Contrast-enhanced magnetic resonance imaging (MRI) is an important tool in monitoring disease activity in patients with this condition. The location, number, size, and enhancement of these lesions are ways in which disease burden is quantified. Active inflammation causes breakdown of the blood brain barrier, allowing gadolinium contrast agents to accumulate and cause T1 shortening (hyperintensity) which may be evident for several months. As a

result, recent disease activity can be identified as areas of both increased T2 relaxation time (hyperintensity) and contrast enhancement (Hemond, May 2018). Evaluation for evidence of active disease is important in assessing response to DMTs. DMTs are a class of treatments for MS which modulate the immune system in a variety of ways with the goal of reducing active inflammation. It has been observed that many older patients can safely stop DMTs in the proper clinical context, specifically after consideration of the length of time without relapse or disability progression. There is recent data that supports this practice, with lack of progression of symptomatic disease on follow-up in certain populations aged 53-55 years and older (Schwehr, Mar 2020; Weideman, Nov 2017).

Imaging without clinical necessity or evidence of benefit has been observed to cause immense burden, both physically and financially (Jahanmer et al, Oct 2019). Regular contrast-enhanced imaging without clear potential benefit can be harmful, especially considering recent developments concerning gadolinium deposition. Nephrogenic systemic fibrosis (NSF) has been extensively documented since being first described in 2006, with gadolinium deposition in the skin and joints resulting in induration, constant pain, and severe disability in those with end stage renal disease (Semelka et al, Aug 2016). Similarly, there has been increasing evidence of gadolinium deposition in the brain, especially in the globus pallidus and dentate nucleus (Semelka et al, Dec 2016). However, any clinical consequence of deposition remains inconclusive, with the only description of a true ‘gadolinium deposition disease’ being observed in patients with a syndrome defined by central and peripheral pain, headache, and clouded mentation, alongside the symptoms seen in NSF (Semelka et al 2016). Nevertheless, this has resulted in pharmaceutical regulatory bodies in Europe, Japan, and Korea modifying recommendations on the use of various gadolinium-based contrast agents (Choi, Jan 2019).

This retrospective study was performed with the goal of assessing the utility of gadolinium contrast-enhanced MRI for older patients with MS after cessation of DMTs. Our hypothesis is that after DMT cessation, follow-up MRI will rarely reveal enhancing lesions. Our secondary objective was to review the frequency in which new lesions and enlarging lesions were encountered.

Methods

Our study was HIPAA compliant and approved by the University of Vermont IRB. We retrospectively identified all head, cervical, and thoracic MRIs performed on patients with a diagnosis (ICD-9 and ICD-10) of MS acquired between 1/1/2005 to 2/1/2021 within the Department of Radiology at the University of Vermont Medical Center. MRIs were included as long as two criteria were met: 1) patient was no longer on DMTs, and 2) patient was older than 55 years of age at the time of the MRI.

All MRIs were performed with either a 1.5 Tesla or 3.0 Tesla magnet (Philips; Andover, Massachusetts, USA). At our institution, the routine clinical MRI of the head using the MS protocol is as follows: axial DWI, pre-contrast 3D T1, axial T2, axial SWI, 3D T2-FLAIR, and post-contrast 3D T1. 3D T2-FLAIR and 3D T1 pre- and post-contrast sequences were available to review in axial, sagittal, and coronal planes. 3D T2-FLAIR sequences had a slice thickness of 1.2 mm, 1.2 mm spacing between slices, repetition time of 4800 ms, echo time of 320 ms, inversion time of 1660 ms, an echo number of 1, and a flip angle of 90 degrees. The 3D T1 post-contrast sequences had a slice thickness of 1 mm, 1 mm spacing between slices, repetition time of 20 ms, echo time of 5 ms, an echo number of 1, and a flip angle of 30 degrees. Our MRI MS protocol for the spine is the same as a routine spine MRI with the addition of a sagittal proton density sequence for improved lesion detection.

For each MRI, the following were obtained: 1) date of the MRI, 2) age of patient at the time of the MRI, 3) study type, 4) magnet strength, and 5) use of contrast. Reports for each MRI were reviewed for the following: 1) number of new T2 hyperintense lesions, 2) number of enlarging T2 hyperintense lesions, and 3) number of enhancing lesions.

Results

A total of 209 MRIs were obtained and reviewed. Gadolinium contrast was administered for a majority, 178/209 (85.2%), of the MRIs. Of the 178 MRIs obtained with contrast, 1 (<1%) described a questionable enhancing lesion in the thoracic spinal cord. None of the MRIs described enhancing lesions

in the brain or cervical spinal cord. There were 27 (12.9%) MRIs that reported new T2 hyperintense lesions. One MRI (<1%) described an enlarging lesion in the ventral pons.

Discussion

The number of MRIs demonstrating new T2 hyperintense lesions (12.9%) may be clinically significant, but not all of the new lesions may be due to MS. There are many pathologies that can cause new T2 hyperintense lesions in the brain parenchyma in older patients (e.g. chronic microangiopathy). Our data supports the ongoing research to identify a method by which new T2 hyperintense lesions can be characterized as that due to MS disease activity or an alternate etiology. Given the frequency in which new, non-enhancing lesions were encountered, the ability to make such a determination is important likely impacts clinical management. Our data demonstrates that enlarging and enhancing lesions, the latter only visible after contrast administration, are rare. The low incidence of enhancing lesions argues that there is a cohort of patients that can be identified for which contrast can be withheld without fear of missing recent disease activity, especially if lesion burden is unchanged. Indeed, in the specific instance in which a questionable enhancing lesion in the thoracic spinal cord was described, the clinical management did not change, and no enhancing lesion was present in the same location on the follow-up MRI. As such, the clinical utility of contrast agents in this patient population is highly doubtful.

Our study has several weaknesses, particularly in its retrospective in design. A prospective trial in which patients are randomized to either imaging with contrast or without would allow better evaluation of the clinical utility of contrast agents. Second, the MRI reports were our primary source of information regarding lesions. We did not independently review images but rather relied on the reports. However, we believe our approach represents that of a typical, real-world scenario in which clinicians may rely on reports for decision-making. Although there may be false negatives and false positives in our cohort, we believe these to be uncommon and unlikely to impact the outcome. Our cohort represents MS patients monitored at a tertiary academic center which may not be representative of MS patients elsewhere. We did not investigate the clinical data for each patient, including length of DMT therapy, reasons for

stopping DMT, and type of DMT. This information could be used to further define any cohort of patients for which contrast administration cessation could be recommended. Finally, our cohort may have been prone to a selection bias. We chose to review MRIs on patients not on DMTs and presumably patients had no clinical and imaging evidence of disease activity. As such, evidence of disease activity (new, enlarging, enhancing lesions) on future follow-up imaging would then be less common. However, our data suggests that enhancing lesions are rare in this cohort, regardless of the clinical context. It follows that if the decision is made to stop DMTs in a patient older than 55, follow-up MRIs could then be performed without contrast.

In conclusion, our findings demonstrate that the discovery of enhancing lesions on a follow-up MRI in a patient with MS, age 55 or older at the time of the MRI, and not on DMTs, is rare. In the single case identified of a questionable enhancing lesion in the thoracic spinal cord, clinical management did not change. No enhancing lesions were ever encountered in the brain parenchyma or cervical cord. Our data suggests that contrast could be safely withheld in this context and future research is needed to corroborate our results.

Citations

Choi JW, Moon WJ. Gadolinium Deposition in the Brain: Current Updates. Korean J Radiol. 2019;20(1):134-147. doi:10.3348/kjr.2018.0356.

Hemond, Christopher C, Bakshi Rohit. “Magnetic Resonance Imaging in Multiple Sclerosis”. Cold Spring Harb Perspect Med. 2018 May; 8(5): a028969. doi: 10.1101/cshperspect.a028969 <https://www-ncbi-nlm-nih-gov.ezproxy.uvm.edu/pmc/articles/PMC5932576/>.

Jahanmehr N, Bigdeli AS, Salari H, Mokarami H, KhodaKarim S, Damiri S. “Analyzing inappropriate magnetic resonance imaging (MRI) prescriptions and resulting economic burden on patients suffering from back pain”. Int J Health Plann Manage. 2019 Oct;34(4):e1437-e1447. doi: 10.1002/hpm.2806. Epub 2019 Jul 4. PMID: 31271228.

Semelka, RC, Ramalhol, Miguel, AlObaidy, Mamdoh, Ramalhol, Joana. “Gadolinium in Humans: A Family of Disorders”. American Journal of Roentgenology. Aug 2016;207: 229-233. 10.2214/AJR.15.15842

Semelka RC, Ramalho J, Vakharia A, AlObaidy M, Burke LM, Jay M, Ramalho M. “Gadolinium deposition disease: Initial description of a disease that has been around for a while”. Magn Reson Imaging. 2016 Dec;34(10):1383-1390. doi: 10.1016/j.mri.2016.07.016. Epub 2016 Aug 13. PMID: 27530966.

Schwehr NA, Kuntz KM, Enns EA, Shippee ND, Kingwell E, Tremlett H, Carpenter AF, Butler

M; BeAMS Study group. “Informing Medication Discontinuation Decisions among Older Adults with Relapsing-Onset Multiple Sclerosis”. Drugs Aging. 2020 Mar;37(3):225-235. doi: 10.1007/s40266-019-00741-1. PMID: 31916231. < Schwehr NA, Kuntz KM, Enns EA, Shippee ND, Kingwell E, Tremlett H, Carpenter AF, Butler M; BeAMS Study group. Informing Medication Discontinuation Decisions among Older Adults with Relapsing-Onset Multiple Sclerosis. Drugs Aging. 2020 Mar;37(3):225-235. doi: 10.1007/s40266-019-00741-1. PMID: 31916231; PMCID: PMC7047543>.

Weideman AM, Tapia-Maltos MA, Johnson K, Greenwood M, Bielekova B. “Meta-analysis of the Age-Dependent Efficacy of Multiple Sclerosis Treatments”. Front Neurol. 2017 Nov 10;8:577. doi: 10.3389/fneur.2017.00577. PMID: 29176956. < https://pubmed-ncbi-nlm-nih-gov.ezproxy.uvm.edu/29176956/>.